

Cassia angustifolia and tacrolimus interaction in a liver transplant patient, a case report

Iván Beltrá-Picó¹, Marcos Díaz-Gonzalez¹, Ricardo Nalda-Molina², Amelia Ramón-López², Sonia Pascual-Bartolomé³, Cayetano Miralles-Macià³, and Patricio Más-Serrano¹

¹Alicante General University Hospital Pharmacy

²Miguel Hernandez University of Elche

³Hospital General Universitario de Alicante

September 6, 2023

Abstract

Cassia angustifolia is a species of a plant from the Senna family that has traditionally been used as a laxative in different herbal products and commercial medicines. There are few described interactions between Senna and drugs, most of them related to electrolyte disturbances due to concomitant use with other laxatives or due to increased intestinal transit that may limit the absorption of drugs with low bioavailability. We present a case with supratherapeutic trough concentration of tacrolimus in a liver transplant patient after concomitant intake of tacrolimus and a herbal product based on Cassia angustifolia, suggesting a possible drug-plant interaction by means of P-glycoprotein. We observe an increase in their plasma concentration 2.8-fold and the AUC 2.1-fold.

I Beltrá-Picó^{1,2}, *M Díaz-Gonzalez*^{1,2}, *R Nalda-Molina*^{2,3}, *A Ramón-López*^{2,3}, *S Pascual-Bartolomé*^{2,4}, *CF Miralles-Macià*^{2,4}, *P Más-Serrano*^{1,2}

¹ Alicante General University Hospital Pharmacy, Clinical Pharmacokinetics Unit Alicante, Comunidad Valenciana, ES

² Alicante Institute for Health and Biomedical Research (ISABIAL-FISABIO Foundation) Alicante, Comunidad Valenciana, ES

³ Miguel Hernandez University of Elche, Pharmacy and Pharmaceutical Technology San Juan de Alicante, Alicante, ES

⁴ Alicante General University Hospital, Hepatology and Liver Unit Alicante, Comunidad Valenciana, ES

Correspondence:

Iván Beltrá Picó, Pharmacy Department, Alicante University General Hospital, 03010 Alicante, Spain.
Email: beltra_iva@gva.es

ORCID

Iván Beltrá Picó <https://orcid.org/0000-0003-4576-8008>

Patricio Más Serrano <https://orcid.org/0000-0002-0547-5975>

Ricardo Nalda-Molina <https://orcid.org/0000-0001-7183-6372>

Amelia Ramón-López <https://orcid.org/0000-0002-2848-4743>

Sonia Pascual-Bartolomé <https://orcid.org/0000-0002-4265-5019>

Cayetano Fabian Miralles Macia <https://orcid.org/0000-0003-2037-6358>

Key words: Food/Herbal drug interactions, Pharmacokinetic-pharmacodynamic, Transplantation, Liver, Immunosuppression.

Words: Table: 1 Graph: 1

What is already known about this subject:

Tacrolimus is a drug with potential risk of metabolism and P-glycoprotein-mediated interactions.

What this study adds:

We describe the first case of *Cassia Angustifolia*-tacrolimus interaction through P-glycoprotein which increased the exposure to tacrolimus. Particularly, in a liver transplant patient.

Our report highlights the need to clinically monitor patients if medicinal plants are added to their therapy.

***Cassia angustifolia* and tacrolimus interaction in a liver transplant patient, a case report**

Cassia angustifolia is a species of a plant from the Senna family that has traditionally been used as a laxative in different herbal products and commercial medicines. There are few described interactions between Senna and drugs, most of them related to electrolyte disturbances due to concomitant use with other laxatives or due to increased intestinal transit that may limit the absorption of drugs with low bioavailability.

We present a case with supratherapeutic trough concentration of tacrolimus in a liver transplant patient after concomitant intake of tacrolimus and a herbal product based on *Cassia angustifolia*, suggesting a possible drug-plant interaction by means of P-glycoprotein. We observe an increase in their plasma concentration 2.8-fold and the AUC 2.1-fold.

CASE REPORT

A 60-year-old Caucasian male, weighing 59 kg, liver transplanted 2 months ago. In the outpatient clinic he was asymptomatic, had normal biochemistry, and tacrolimus trough concentrations within the therapeutic range (7.2 ng/mL and an estimated area under the curve is steady state (eAUC) of 245 ng·h/mL) (Table 1). He was on prophylactic treatment with tacrolimus (extended-released capsules) 8 mg qd, mycophenolate mofetil 1000 mg bid and prednisone 5 mg qd. His oral medication at home included: magnesium 53 mg tid, hydrophorol 0.266 mg, furosemide 40 mg bid, cotrimoxazole 400/80 mg qd, nystatin and pantoprazole 20 mg qd.

Fifteen days after the outpatient visit, he was admitted to hospital with signs of respiratory infection and was diagnosed of empyema secondary to *Enterobacter cloacae* infection. At admission, the patient presented with significant renal impairment (creatinine clearance (CrCl): 27.9 mL/min/1.72 m²) with a tacrolimus trough concentration of 20.5 ng/mL and an eAUC 524 ng·h/mL, consistent with the nephrotoxicity associated with supratherapeutic exposure to tacrolimus (Table 1). Correct veno sampling were ensured and no changes were made in the tacrolimus determination technique (enzyme-linked immunosorbent assay (Dimension)), or to the commercial presentation of the tacrolimus prescribed to the patient. No relevant changes in the prescribed treatment were identified that could affect the bioavailability or pharmacokinetics of tacrolimus.

After interviewing the patient, he reported a daily intake of an over-the-counter (OTC) herbal laxative for several days taken concomitant with tacrolimus first time in the morning. The OTC is composed of 80% senna leaves (*Cassia angustifolia vahl*), hibiscus extract, liquorice (*Glycyrrhiza glabra*) and peppermint (*Mentha piperita*). The herbal preparation and tacrolimus treatment were discontinued until tacrolimus plasma concentrations normalized.

A trough of 5 ng/mL was reached three days after drug withdrawal. Tacrolimus treatment was then gradually reintroduced. The dose was increased using individual pharmacokinetic parameters calculated by Bayesian

estimation (Graph 1). One week after tacrolimus intoxication and after discontinuation of herbal medicine, the patient recovered baseline renal function (ClCr 81.9 ml/min/1.72 m²) and achieved tacrolimus target levels at a dose similar to that before the episode (Table 1, Graph 1).

DISCUSSION

Senna (*Cassia senna*) is commonly used as a laxative in different herbal-based medicines. Both its leaves and pods contain active ingredients of an anthraquinone nature, mainly Sennosides A and Sennosides B (hydroxyanthracene heterosides). These undergo bacterial hydrolysis and subsequent metabolic reduction in the large intestine, where they are converted into active metabolites in the form of rhein anthrone (1). It is classified as a contact or stimulant laxative; its activity is based on two different mechanisms of action. On the one hand, by direct stimulation of the nerve plexus in the large intestine mucosa, which increases peristalsis. On the other hand, it modifies fluids and electrolytes absorption in the colon, and appears to have a secretory effect (1).

In the large intestine, *in vitro* models have shown that sennoside metabolites undergo a significant secretory activity, probably mediated by efflux pumps (2), which limits its passage into the plasmatic circulation. The vast majority of sennosides are excreted via the feces (approximately 90%), and the metabolites that reach plasma circulation are excreted via the kidneys and bile. Cytochrome-mediated hepatic metabolism has not been described. There are few described interactions between Senna and drugs, most of them related to electrolyte disturbances due to concomitant use with other laxatives or due to increased intestinal transit that may limit the absorption of drugs with low bioavailability (3, 4).

Tacrolimus is an anticalcineurin drug, with a narrow therapeutic index, used as an immunosuppressant in the prophylaxis and treatment of renal, hepatic, and cardiac graft rejection. Tacrolimus is metabolised mainly through CYP3A4 and CYP3A5 in the liver and intestine and to a lesser extent by CYP2C19. Mainly in the intestine, tacrolimus is a substrate for efflux pumps such as P-glycoprotein (P-gp) (4). Several interactions between tacrolimus and various phytotherapeutic compounds have been described. Those that are inducers of CYP3A4 and P-gp (e.g., *Hypericum perforatum*) have been shown to significantly reduce considerably the plasma concentrations of tacrolimus. Whereas those that act by inhibiting CYP3A4 and P-gp (e.g., *Citrus paradisi* or *Citrus grandis* "grapefruit juice", *Curcuma longa*, etc.) increase the plasma concentrations of the immunosuppressant (5). Previous studies have shown P-gp substrate concentration-dependent saturation with cyclosporine (6) or taxanes (7). Although the P-gp inducers have not shown relevant effects, its inhibition or saturation, as hypothesized in this case, could be clinically relevant (8). Administration of a single dose of verapamil (potent P-gp inhibitor) one hour before or concomitantly with dabigatran exilate (P-gp substrates drugs not related to CYP metabolism) increased AUC 2.4-fold and 2.1-fold respectively (9). Concomitant administration of two substrates may saturate the efflux pumps, increasing the exposure to both drugs. The administration of the immediate or extended-release tacrolimus formulations, which reach their C_{max} between 1-3h, makes the interaction more likely. The clinical impact of the interaction is based on the saturation of the efflux pumps in the absorption phase of tacrolimus, reducing its expulsion into the intestinal lumen before entering to plasmatic circulation.

Although the percentage of *Glycyrrhiza glabra* and *Mentha piperita* present in the herbal preparation is negligible compared to that of Cassia, the potential interactions with tacrolimus that could have clinical relevance were revised.

Glycyrrhiza glabra, traditionally known as a specie of licorice, is a plant of the *Fabaceae* family, whose roots are used as a traditional remedy in the treatment of dyspepsia and peptic ulcers. It is important to differentiate the species of licorice because there are substantial differences in its constituents and their interaction profile varies. Although there are discrepancies, recent data suggest that it acts as a weak inhibitor of CYP3A4 and CYP2C19 (10, 11), probably without clinical relevance. In addition, *Glycyrrhiza glabra* acts as an inhibitor of P-gp, causing an increase in the intracellular concentration of daunorubicin, which is a substrate of P-gp (12), unlike *Glycyrrhiza uralensis* whose major component glycyrrhizin has shown the opposite effect (13). Regarding the other component of the herbal preparation, the leaves of *Mentha*

piperita traditionally known as peppermint (a plant of the *Labiatae* family) have been traditionally used for digestive disorders as a spasmolytic, antiemetic and sedative. In vitro studies suggest a weak inhibitor effect on the metabolism mediated by CYP3A4 and a stronger one on that mediated by CYP2C19 (14, 15).

In this case, we suggest that the sennosides act by saturating the efflux pumps, reducing the excretion of tacrolimus, which decreases its clearance by 80% when administered at the same time. We observed a 2.8-fold increase in their plasma concentration and a 2.1-fold increase in AUC. A metabolism interaction by *Glycyrrhiza glabra* or *Mentha piperita* is unlikely to have a clinical impact due to their low proportion in the herbal preparation and their interaction profile, but we cannot rule it out due to the significant increase in exposure. The rapid recovery of clearance after the suspension of the herbal preparation suggests that it is not an enzymatic inhibition. Further studies are needed to analyze the relationship between efflux pumps and sennosides.

AUTHOR CONTRIBUTION:

BP and MS interpreted data. BP, MS, DG, NM, RL wrote the original draft. BP and MS performed the pharmacokinetic analysis. All authors revised the manuscript. All authors approved the final version of the manuscript.

FUNDING:

This report received no special funding.

COMPETING INTERESTS:

The authors have no conflicts of interest to declare.

ETHICAL APPROVAL:

Not applicable.

DATA AVAILABILITY STATEMENT:

Additional data are available from the corresponding author upon reasonable request.

1. Ulbricht C, Conquer J, Costa D, Hamilton W, Higdon ER, Isaac R, et al. An evidence-based systematic review of senna (*Cassia senna*) by the Natural Standard Research Collaboration. *J Diet Suppl.* 2011;8(2):189-238.
2. Waltenberger B, Avula B, Ganzera M, Khan IA, Stuppner H, Khan SI. Transport of sennosides and sennidines from *Cassia angustifolia* and *Cassia senna* across Caco-2 monolayers—an in vitro model for intestinal absorption. *Phytomedicine.* 2008;15(5):373-7.
3. Fugh-Berman A. Herb-drug interactions. *Lancet.* 2000;355(9198):134-8.
4. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. *Clin Pharmacokinet.* 2004;43(10):623-53.
5. Abushammala I. Tacrolimus and herbs interactions: a review. *Pharmazie.* 2021;76(10):468-72.
6. Saeki T, Ueda K, Tanigawara Y, Hori R, Komano T. Human P-glycoprotein transports cyclosporin A and FK506. *J Biol Chem.* 1993;268(9):6077-80.
7. Cisternino S, Bourasset F, Archimbaud Y, Semiond D, Sanderink G, Scherrmann JM. Nonlinear accumulation in the brain of the new taxoid TXD258 following saturation of P-glycoprotein at the blood-brain barrier in mice and rats. *Br J Pharmacol.* 2003;138(7):1367-75.
8. Akamine Y, Yasui-Furukori N, Uno T. Drug-Drug Interactions of P-gp Substrates Unrelated to CYP Metabolism. *Curr Drug Metab.* 2019;20(2):124-9.

9. Hartter S, Sennewald R, Nehmiz G, Reilly P. Oral bioavailability of dabigatran etexilate (Pradaxa((R))) after co-medication with verapamil in healthy subjects. *Br J Clin Pharmacol.* 2013;75(4):1053-62.
10. Li G, Simmler C, Chen L, Nikolic D, Chen SN, Pauli GF, et al. Cytochrome P450 inhibition by three licorice species and fourteen licorice constituents. *Eur J Pharm Sci.* 2017;109:182-90.
11. Nazari S, Rameshrad M, Hosseinzadeh H. Toxicological Effects of Glycyrrhiza glabra (Licorice): A Review. *Phytother Res.* 2017;31(11):1635-50.
12. Nabekura T, Yamaki T, Ueno K, Kitagawa S. Inhibition of P-glycoprotein and multidrug resistance protein 1 by dietary phytochemicals. *Cancer Chemother Pharmacol.* 2008;62(5):867-73.
13. Hou YC, Lin SP, Chao PD. Liquorice reduced cyclosporine bioavailability by activating P-glycoprotein and CYP3A. *Food Chem.* 2012;135(4):2307-12.
14. Unger M, Frank A. Simultaneous determination of the inhibitory potency of herbal extracts on the activity of six major cytochrome P450 enzymes using liquid chromatography/mass spectrometry and automated online extraction. *Rapid Commun Mass Spectrom.* 2004;18(19):2273-81.
15. Dresser GK, Wachter V, Wong S, Wong HT, Bailey DG. Evaluation of peppermint oil and ascorbyl palmitate as inhibitors of cytochrome P4503A4 activity in vitro and in vivo. *Clin Pharmacol Ther.* 2002;72(3):247-55.

Hosted file

Table 1.docx available at <https://authorea.com/users/660150/articles/663831-cassia-angustifolia-and-tacrolimus-interaction-in-a-liver-transplant-patient-a-case-report>

Hosted file

Graph 1.docx available at <https://authorea.com/users/660150/articles/663831-cassia-angustifolia-and-tacrolimus-interaction-in-a-liver-transplant-patient-a-case-report>